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U.S. Environmental Protection Agency
Science Advisory Board
Environmental Health Committee (EHC)
Trichloroethylene Health Risk Assessment: Synthesis and Characterization Review Panel

Summary Minutes of Public Meeting
Date: June 18-19, 2002

Panel Members: (See Roster - Attachment A.)
Date and Time: 9 am to 5:15 pm, June 18, 2002 and 9 am to 2:30 pm, June 19 (See Federal Register Notice - Attachment B).
Location: RESOLVE, 1255 23rd Street, Suite 275, NW Washington, DC 20037
Purpose: The purpose of this meeting was to conduct a review of an Agency draft document, Trichlorethylene Health Risk Assessment: Synthesis and Characterization, Draft Report, Prepared for the U.S. Environmental Protection Agency, Office of Research and Development, EPA/600/P-01/002A, August 2001 External Review Draft. The Review Panel met to: (1) engage in dialogue with appropriate officials from the Agency who are responsible for its preparation; (2) begin to prepare responses to the charge questions; (3) receive public comments as appropriate; and (4) plan the process needed to complete this review.

Attendees: Chair: Dr. Henry Anderson; Panel Members: (EHC Members) Dr. Dale Hattis, Dr. David Hoel, Dr. George Lambert, Dr. Grace LeMasters, Dr. Abby Li and Dr. Ulrike Luderer; (SAB Consultants) Dr. Susan J. Borghoff, Dr. Lutz Edler, Dr. Michael McClain, Dr. Gina Solomon; (Federal Experts) Dr. Aaron Blair, Dr. Ronald Melnick, and Dr. Raymond Yang

EPA SAB Staff: Dr. Angela Nugent, (DFO for the Panel), Ms. Arlene Black; Ms. Diana Pozun (Management Assistant for the Panel), and Dr. Vanessa Vu.

Other Persons Attending: Dr. V. James Cogliano EPA, Office of Research and Development; speaker noted on the agenda); oral public commenters, as noted on the agenda, and other members of the public, as noted on the sign-in sheet (Attachment C).

Meeting Summary:

The discussion generally followed the issues and general timing as presented in the meeting Agenda (see Meeting Agenda - Attachment D). The meeting lasted until 5:15 pm on June 18, 2002 and until 2:30 pm on June 19, 2002. There were two sets of written comments submitted to the Panel and eleven written requests to present public comments during the meeting.

Welcome and Introductions:

Dr. Henry Anderson, the Chair, opened the session at 9:00 am welcoming panel members (Roster, Attachment A), and reviewed the agenda (Attachment C). Dr. Angela Nugent, Designated Federal Official (DFO) described the process used by the EPA SAB staff in forming the panel. She stated that the SAB Staff followed the a new process for forming panels that was described in the draft

document "Overview of Panel Formation at the EPA Science Advisory Board" (Attachment E) and detailed in a document on the SAB website "US EPA Science Advisory Board (SAB) Trichloroethylene Health Risk Assessment: Synthesis and Characterization Review Panel (TCE Review Panel) documentation for Panel Formation Determinations." She stated that members had described their background, expertise, and activities relating to the panel's topic in written "Biosketches" (Attachment F) that were posted on the SAB website and available to the public at the meeting.

Members of the panel briefly introduced themselves and their institutional affiliations.

Dr. Vanessa Vu, Director of the SAB Staff welcomed the panelists and thanked them for the service on the panel. She disclosed her past role as Deputy Director of EPA's National Center for Environmental Assessment, where she provided oversight of the development of the draft assessment. She stated that she had no involvement in the draft since May 2001 and that she had recused herself from discussions and decisions about selection of panel members.

Dr. Anderson then launched the review by reminding panel members that their job was specifically to provide concrete suggestions for improving the review.

Discussion of Agency Goals for the Review:

Dr. V. James Cogliano provided some brief background on the development of the draft assessment. He described the unusual process adopted by the Agency, since there was so much new data on TCE and a wide range of views about so them. He stated that the may 2000 special issue of Environmental Health Perspectives, represented "State of the Science" papers from a wide range of authors. As EPA developed its draft document, it asked "State of the Science" authors individually to review the draft and also shared the draft with stakeholders. The document was released in August 2001 for public comments.

In his view, the public comments received were similar in topics and range of views as those expressed by the "State of the Science" authors.

These wide ranges of viewpoints were helpful to the Agency as it addressed a variety of new issues for risk assessment within the specific context of the TCE assessment. He described how the assessment attempted to deal with many different kinds of data on cancer (e.g., VH1 gene, phenotypes of TCE tumors, mode of action, toxicokinetic modeling), and not just tumor endpoints. In this draft assessment, the Agency sought to address the controversy that had existed since 1989, when the Agency's consensus workgroup, the Integrated Risk Information System (IRIS) workgroup, could not determine if TCE should be classified as a "B2" or "C" carcinogen. This lack of certainty reflected the differing views at that time of the American Conference of Governmental Industrial Hygienists and the International Agency for Research on Cancer.

The Agency also sought to in the assessment to address issues of sensitive subpopulations, especially children, since the database for TCE contains more information than for any chemical other than dioxin.

Dr. Cogliano then responded to the Panel's request at its June 5, 2002 teleconference call for information on general risk assessment guidance being

developed by EPA that is related to the TCE draft assessment. In regard to the cancer guidelines, he stated that EPA had issued a Federal Register notice in November 2001 informing the public of the Agency's intent to update the cancer guidelines in 2002. The Agency also announced that in the interim, it would use the 1999 draft guidelines. Dr. Cogliano stated that EPA intends to use for the final TCE assessment whatever version of the cancer guidelines is in effect when the assessment is finalized.

He also provided the panel with information on the Agency's final guidance on mixtures (July 2001) and an update on the process of developing guidance on the RfD/RfC setting process. He stated that the Agency had issued a draft RfD guidance document last month and was holding a peer review meeting simultaneous with the TCE review. He noted that there were some recommendations in that draft document that were relevant to the TCE assessment: (1) all relevant endpoints should be considered; (2) in regard to polymorphism, a ten-fold factor is sometimes too small; and (3) encouragement to evaluate susceptible populations, such as children and the elderly.

He also noted that the Agency's draft cumulative risk framework as posted on the EPA website last month. He clarified the differences between aggregate and cumulative risks (aggregate risk refers to exposures to one stressor from multiple sources and/or multiple pathways; cumulative risk refers to exposures from multiple stressors; cumulative risk encompasses chemical and non-chemical stressors).

He then responded to a specific question about the neurotoxicity studies considered in the review. He noted that Agency for Toxic Substances and Disease Registry (ATSDR) had based its uncertainty factors for neurotoxicity on a study by Arito. EPA used the same study with others to derive an assessment of chronic neurotoxicity effects.

Dr. Cogliano then turned to the Agency’s goals for the panel’s review. He asked the panel to review the draft assessment to identify the critical issues. Where science allows resolution of issues, he asked the panel to identify those cases; where there are different data or scientific approaches, he asked the panel to consider whether the assessment frames the issues so that readers can see the different scientific viewpoints and reach their own conclusions. He specifically asked the panel to consider the Agency’s use of uncertainty analysis and modeling and how it addressed the issue of susceptibility and cumulative risk.

Discussion of Charge Question 1: Does the assessment adequately discuss the likelihood that trichloroethylene (TCE) acts through multiple metabolites and multiple modes of action?

The lead discussant began by commending the Agency’s qualitative treatment of a wide variety of causal hypotheses for the carcinogenic and other toxic effects of TCE. He suggested that the document could be enhanced by quantitative analyses on these points that would: (1) compare observed liver cancers with those predicted in models; (2) compare tumor characteristics induced by DCA with those induced by TCE; (3) examination of the correlation between the peroxisome proliferation potency and apparent carcinogenic potency of TCE and its metabolites across species, genders, etc.; (4) quantitative analysis of the correlation between mutagenic potency in specific test systems used for TCE and its metabolites and carcinogenic potencies for chemicals as

conventionally determined by EPA--this analysis would assist the Agency in evaluating genotoxic contributions to carcinogenic action in the liver.

Other panelists agreed. One stated that it was critical to quantitate DCA to understand the mode of action. There was a call for a table showing modes of action of metabolites present in liver tissue as well as a call for a table showing tumor type by metabolite. Another panelist called for a quantitative examination of metabolite interaction. He said the risk assessment was a "mixture study" and necessarily raised "mixture concerns" that needed to be addressed quantitatively. Yet other panelists said that the document presents no clear indication about how suggested modes of action relate to dosimetry or how doses relate to modes of action.

A panel member commended the Agency for taking on the difficult challenge of examining multiple modes of action. He suggested the chapter discussion was too diffuse and that it needs a summary paragraph that articulates the Agency's position on critical metabolites, mode of action, and the science basis for these conclusions.

The panel member also noted that whenever there is a possibility of multiple substrates sharing metabolic pathways, the authors always suggest that toxicity will increase. He stated that the situation was more complicated. If TCE concentration increases because of competition from other chemicals, potentially sensitive pathways could be favored, if TCE decreases because of competition from other chemicals, the toxicity may decline. The panel member advised the Agency to develop a table showing the comprehensive metabolic pathways illustrated with metabolites sharing those pathways quantitated.

The panel member also suggested that the draft assessment reference original papers, and not the "state of the science" papers, wherever possible.

Another panel member remarked that she found the mode of action discussion refreshing because it moved beyond the convention one-chemical, one-mode-of-action assessment and was "more realistic." This view was echoed by another member, who stated the Agency did a good job delineating the complexities of multiple modes of action and describing the associated uncertainties in the analysis.

The Chair then asked the panel for their major suggestions for improving quantification. One panelist responded that EPA could analyze the data it already has quantitatively, and that the Agency needed to develop and foster habits of asking questions in "quantitative distributional ways." He urged the Agency not to simply classify results as "positive or negative." But instead "use the data available." Another panelist offered the vision of EPA investing in a major way in physiologically based pharmacokinetic modeling. He said that it is the future of risk assessment, "as we improve our knowledge in these areas, virtual human and virtual rat will become more realistic." Another panelist said that she "tended to think of dose as mode of action; that's why establishing dosage is so crucial. Mode of action can't 'happen' until quantitation is established." Another panelist added that modelers needed to be guided by the research of biologists' regarding metabolic action. A colleague responded that carcinogenicity of the liver might be the most complex and useful focus for research to determine whether TCE in lever starts with DCA and TCA? Or through both mechanisms? Or in some other way?

Discussion of Charge Question 2: Is the cancer weight-of-evidence characterization adequately supported?

The Lead Discussant led off by noting the paradoxical situation of the extraordinarily rich scientific database for TCE and yet the frustrating gaps in studies and information. She noted that in that context, EPA did an extraordinarily good job of characterizing the data coherently and making tough decisions. She noted that the Agency carefully discussed and considered a variety of evidence (epidemiological evidence, in vitro studies, mode of action, and pharmacokinetics) and did not rely on any of those pieces exclusively.

She then listed her principal concern about the cancer assessment: renal cancer. She noted that the Henschler study injected considerable heterogeneity into the Wartenberg analysis. She acknowledged the concern from public commenters over this, but informed the group that she ultimately came to agree that the Agency should include both the Henschler study and the Wartenberg analysis, because such an approach used available evidence and the flaws were "not fatal flaws." She considered that workplace cluster investigations, like the Henschler study, were instrumental in risk assessment/risk management approaches for key carcinogens, such as vinyl chloride and angiosarcoma. She also became convinced, that exposures were very high in workplaces studied in Henschler, and that those workers were "higher on the dose response curve." She stated that "when epidemiology studies pick something shown by the animal literature, we should pay attention."

She said that the cancer assessment was "crying out for a meta-analysis and it's not there" and that some kind of formal or informal meta-analysis should be done. She recommended that the recent Hansen study be included. She also recommended that the discussion of Non-Hodgkins lymphoma and leukemia, especially childhood leukemia be strengthened.

Finally, she believed the designation of "highly likely" to cause cancer was well supported. The animal literature is very strong. The epidemiology literature is stronger than what we almost always see. She believed the data on the chemical could almost support a “known” designation.

The Associate Discussant for human studies stated that he generally agreed with the Lead Discussant and especially agreed that meta-analysis should be done; the "only time not to do it is when it’s so simple, you don’t do it." He suggested that the analysis focus only on the Tier 1 studies identified in Wartenberg and other studies where effects were "reasonably linked to TCE." He believed that most Tier 2 and Tier 3 studies were not relevant.

The Associate Discussant for animal studies stated that he first examined how tumors were related to treatment. In the rat, he found there was a low incidence of kidney cell tumors that was unusual but not statistically significant. He saw testicular tumors in all studies that he believes are treatment related. In the mouse liver, he saw a low incidence that he believed was treatment-related. In the mouse, he saw lung tumors that were treatment related and lack of a clear outcome for lymphomas, although the National Toxicology Program has noted concerns. He recommended that EPA reconsider the

lymphomas to see if they were treatment related and consider giving this topic a fuller discussion.

He then asked whether the compound "is genotoxic or not?" He said the "state of science" papers, with the exception of DDC in kidney cannot exclude a genotoxic mode of action for all the target tissues. There is, however, general agreement that metabolites TCA and DCA can account for the toxicity effect in the liver.

In the kidney, the mechanisms could be peroxisome proliferation, DNA damage, cell proliferation, or other mechanisms. He spoke of the difficulties tracing the logic of the Agency's argument in the risk assessment because the citations there primarily relied on the "State of the science" papers, which were literature reviews, not primary references.

In regard to cancer in the liver, the draft assessment supports the conclusion that TCA and DCA are contributing to liver cancer. Although quantities of DCA are not available, modeling shows that it can be there in sufficient concentration. He suggested that the draft analysis state that TCA and DCA promote tumors, as well as acknowledge other modes of action, such as mutagenicity.

In regard to lung cancer, tumors form only through the inhalation route by metabolism of chloral hydrate in clara cells. He said that the draft assessment incorrectly discussed a direct link between clara cells and tumors, although cytotoxic and mutagenic effects may be involved. He said that no direct link between clara cells and tumors had been established.

In concluding his discussion of modes of action, he stated that the section was "difficult to read" but overall reasonable.

The "tough question," however, was not modes of action, but instead the relevance of tumors. The draft assessment concludes that all modes of action are relevant to humans. He thinks instead, that there will be legitimate scientific difference on the pulmonary, liver, and testicular tumors. He thinks the kidney tumors are relevant. In his view, the document dismisses a variety of views too summarily and doesn’t reflect the "state of the science" documents. While the treatment is thorough, it could use more balance.

The Associate Discussant also suggested that dosage needed more attention. He pointed to a "state of the science" article by Bull, which pointed out that a chemical is unlikely to be carcinogenic at low dose, even though carcinogenic at high. The Associate Discussant suggested the Agency outline the data for which tumors were relevant at which dosages and, in parallel, outline areas where there is legitimate scientific debate.

Other panelists joined the discussion. One agreed that the Agency should focus on Tier 1 papers. He noted that the Henschler study has attracted attention as an outlier, but also presents problems because it doesn't discuss liver effects. He also pointed out the difficulty comparing Henschler's results against national baselines for cancer incidence, because of the volatility of those baseline statistics for different countries where the key epidemiology studies were performed. He also noted that the new Hansen study has "nothing on the kidney and has liver."

He also noted that readers should be careful in reading meta-analyses, because numbers extracted from studies for such analyses are often adjusted and

may not be comparable across studies. He also cautioned that meta-analysis requires that studies be heterogeneous; and if one does indeed use a mixed model, one finds, the overall tier 1 incidence is 1.67 with a very wide confidence interval. Another consideration is that such meta-analyses do not generally include negative results, and so factoring in positive incidences creates a kind of "publication bias.

Another panelist noted the improvement in epidemiology studies since IARC's work in 1995, which relied on animal data, because epidemiological data were limited. He concluded from the Wartenberg study, that there was consistency of findings in the liver and hematapoetic systems. To those who suggest "Throw out the Henschler study," he answered: can we conclude it's not due to TCE? He suggested that the most appropriate response would be to work with that evidence.

In regard to some Tier 2 and 3 studies, he is concerned about the suggestion to disregard studies of perclorethylene, because "perc" and TCE form the same pathways and have a similar "signature of exposure" in the VHL genes.

Another panelist noted that the Henschler study presented very high values that are almost outliers. He suggested that the time period during which the subjects were exposed predated many of the other studies and that the population exposed remained "for life in one company." This information could explain the higher values. He also agreed that a true meta-analysis could very well clarify things.

Another panelist suggested that quantitative analysis could help clarify the situation. The Bruning control study of glutathione transferace compared people with renal cancers exposed to TC with people with TCA exposure who didn't develop cancer. Such a study that examines the pathways for kidney cancer – adds to the weight of evidence for kidney cancer.

Another panelist stated that the document needed to discuss more fully the debate in the scientific literature and justify its conclusions. Specific areas she noted that need attention were: (1) validity of studies that originated in cancer cluster; (2) significance of Henschler study as an outlier; (3) gaps in knowledge of exposures for key epidemiology studies.

Another panelist called for a clearer exposition of the findings in the epidemiology study by tumor type, by exposure, so that the reader will understand the key body of evidence (Henschler findings positive for liver but not kidney; the Finnish study shows high levels in liver, but not kidney)

Another panelist echoed this view and emphasized the importance of making the Agency's logic for the "weight of evidence" very clear.

The Lead Discussant then summarized the sense of the group. The panel generally supported the Agency's conclusions as adequately supported by the weight of evidence, taken as a whole. She noted debate on several issues: (1) whether to do meta-analysis on the epidemiological data (one side stated it was desirable; the other side stated the data were too heterogeneous); (2) inclusion of the Henschler study; there were several concerns about it and issues about how much it should be weighted; (3) some key studies needed to be reexamined; and (4) there were differences about the kidney cancer epidemiology and how much decisions about the epidemiology should be informed by the toxicology findings.

There were areas of agreement: (1) interest in more discussion of lymphoma; (2) interest in more discussion childhood leukemia; (3) agreement that Tier 1 and case-control studies should get the most weight (but some disagreement about how to treat tier 2 and 3 studies; some felt the connection to studies of other solvents was not there; others felt including them might set a bad precedent for other chemicals if we don't include them for TCE); (4) agreement that the - genotoxic endpoint mode of action should be discussed more explicitly in the document, that it can't be excluded or dismissed even though evidence is mixed. There was no disagreement with the Agency's draft cancer classification as "highly likely."

Panel members then raised several issues. One asked for guidance on cancer classifications from most recent guidelines. The Chair asked Dr. Cogliano to provide this information later, and asked the panel either to provide clear consensus view on the Agency's cancer classification, or provide advice on how the Agency justified the scientific basis for the decision it made.

Another panel member asked that the Agency provide better documentation for its conclusions than the "state of the science" articles, some of which "distilled down" the sense of the original articles. The Lead Discussant than asked whether the panel wanted the assessment to reference all primary literature. The Chair responded that it would be reasonable to ask the Agency to list key studies relevant to some critical issues, but not to require original citations to all documents. Other panel members concurred.

Another panel member asked that the consensus reflect the suggestion that any meta-analysis include negative findings or a discussion of how negative findings could affect the meta-analysis. He also added that the draft assessment should emphasize Bruning's weight of evidence.

(The Panel took a break for lunch and returned for a session of oral public comments)

Public comments:

The panel then listened to 11 public comments as described in the agenda. Public commenters provided brief presentations, fully summarized by the slides in Attachment G.

Short Discussion of EPA's Cancer Guideliens:
(The Panel decided not to place the call to an independent expert, as planned on the Agenda, and instead asked for a short discussion of EPA's cancer guidelines from Dr. Cogliano.)

Dr. Cogliano explained that EPA issued a Federal Register notice in November 2001 stating its intent to use the 1999 guidelines until new guidelines are approved. EPA is presently revising its Guidelines. The July 1999 draft is available on EPA's website. He briefly outlined the five cancer "descriptors" but asked the panel not to "get tied up" in discussions of these classifications. Instead, he emphasized the value of the panel's advice on how to weigh different lines of evidence, "how to put story together for different

kinds of guidance."

He reiterated the Agency's commitment to use whatever cancer guidelines are in effect, as it finalizes the TCE assessment.

Discussion of Charge Question 3: A new feature of the cancer database is molecular information on the von Hippel-Lindau tumor suppressor gene. Is this information adequately discussed and are the conclusions appropriate?

The Lead Discussant stated that the Agency's discussion is strong and that it is appropriate to call for strengthening the line of evidence concerning the role of this gene by reproducing the relevant study. The existing evidence is very compelling. The simplest way to interpret the evidence is as a direct product of genetic action. Alternative hypotheses need to be explored, including competing hypotheses involving mutagenic action.

The Associate Discussant agreed that there was compelling evidence of a "hot spot." There is a need for replication and background research on whether there's a total increase in VHL.

Other panelists then discussed the issue. One asked whether the tumor suppressor gene was related to the carcinogenic process as an "inactivating mutation." One other issue came up in his mind: tumors with mutations are associated with heterozygotacy; there was a clonal expansion of cells with the VHL gene. He saw this mutation as Consistent with the behavior of the tumor suppressor gene being see as an effect, not a biomarker of exposure.

Another panelist then asked if a mutation occurred, wouldn't the effect be considered genotoxic?

The Chair then asked about the significance of the research needed to replicate the VHL gene effect. He suggested the research could provide a critical piece of information to understand the kidney issue; it would be important to compare groups of people with and without the VHL gene.

Discussion of Charge Question 4: Does the assessment adequately discuss the use of multiple critical effects in developing an oral reference dose (RfD) and inhalation reference concentration (RfC) for effects other than cancer? Are the uncertainty factors well discussed and well supported?

The Lead Discussant began by emphasizing several key points: (1) the importance of examining multiple critical endpoints; (2) the choice of a significant endpoint; (3) the choice of the most sensitive endpoint; and (4) the need for systematic analysis, consistent with biological understanding in accomplishing the previous points. She expressed concern over the Agency's approach in taking multiple endpoints and applying one uncertainty factor. She suggested that the Agency instead consider the critical endpoints, work each such endpoint through logically, discuss the effects, strengths and weakness of studies, and provide the reader with a better understanding of the overall weight of evidence.

She noted that in Tables 4.2 and 4.3 new studies were discussed in the context of dose/response that weren't discussed in the hazard identification section. She presented a review of the neurotoxicity discussion. Table 4.2. cited Arito as the key neurotoxicity study, it was not discussed in neurotoxicology study section. Similarly, Moser et al. was cited in Table 4.2. but not discussed earlier.

She noted public comment regarding the lack of sensitive endpoints, and saw the need for the draft assessment to show both positive and negative studies. She called for the text to explain endpoints, dose levels, time duration, and results. She called on the Agency to use the evaluation criteria from the Agency's recent draft RfD and RfC guidance in its Assessment.

She then turned to the derivation of RfC and RfD and found the logic not clear. She suggested that the derivation of benchmark dose needed a whole section, not just a footnote. She found that the uncertainty factors used for RfD not consistent with RfC, but not explained.

She then turned to the issue of uncertainty factors. Although the issue of background exposure to TCE or metabolites is important, she did not think there should be an uncertainty factor for cumulative risk. Instead, such consideration should be included in a risk characterization, specific to background of a particular exposure scenario. She suggested that a narrative in the text alerting risk managers to the need to consider background exposure, especially where excessive.

The topic of human variation came next. The Lead Discussant didn’t understand how the uncertainty factor made sense for adjustments of liver weight to body weight (such a factor, in her view was appropriate for animal to humans adjustments). She stated that the Barton and Clewell information indicated that humans are "more like rats than mice," and they are not more sensitive than the most sensitive rodents. In the face of these findings, she suggested that the Agency needed to justify taking a different position.

She stated that for converting from rodents to humans, an uncertainty factor was inappropriate generally, although it might be appropriate for a specific endpoint.

She then discussed the use of medications and presence of disease as an uncertainty factor. She said that there was no evidence suggesting that cumulative exposure should be built into an uncertainty factor.

One of the Associate Discussants then began her comments. She noted that the EPA had summarized a wealth of epidemiological and toxicological studies to identify multiple critical effects, and then identified different doses where effects occur in different organ systems. She then stated that she also had difficulty with the manner in which information on these effects were presented. She reiterated the point that Tables 4.2 and 4.3. listed critical studies that had not been described in the section on hazards, which should contain information on why those studies had been chosen and their strengths and weaknesses. In addition, she noted that the Table was 4.X confusing. Column 4 shows experimental doses, but the reader cannot tell which LOEL or NOEL goes with which endpoint.

She also noted that Section 3.4.5 on developmental and reproductive effects needs more detail. It is not apparent which studies look at which compounds (e.g., DCA, TCA or TCE). She called for separate subsections on

each, to follow the TCE discussion. She noted that the section only included cursory references to dev studies that had negative effects; they were dismissed as not relevant, not explained.

She suggested a more extended discussion of uncertainty factors, and found the uncertainty factors a composite number that was problematic. In some cases, readers would apply an uncertainty factor from a NOEL to a LOEL. This problem is unavoidable, given composite uncertainty factors from multiple studies.

In regard to factors to account for human variation, she supported the use of a ten-fold factor for human variation, for LOEL to NOEL conversion. She also suggested that the Barton and Clewell benchmark doses should also be listed. .

The Associate Discussant saw a problem using human epidemiological studies as critical studies to establish benchmark concentrations; she believes studies should be seen as supportive, because they typically don't have good exposure measurements.

Other panelists then contributed their thoughts and generally agreed there should be a in the text of key studies listed Tables 4.2 and 4.3 One panelist noted that the cardiac malformation endpoint deserves more attention in the document, because of positive studies in the avian model, and rodent studies with DCA and TCA, combined with community based epidemiology studies.

Panelists discussed the issue of different uncertainty factors for RfDs and RfCs and the lack of clear explanation for the difference.

Panelists were not agreed on whether to combine or separate endpoints to establish combined uncertainty factor for all endpoints together. One noted a benefit in increasing confidence in looking at all the endpoints as a grouping a creating a "low-dose jumping-off point". She termed it a "judgment call that could go either way," and acknowledged a problem in choosing uncertainty factors as defaults.

The same panelist noted that the uncertainty factor for children's effects was insufficiently developed, and could instead be better driven by data. Children, for example, metabolize TCE four to five times more quickly than adults. She noted that EPA raised relevant points in the document but didn't actually use data. The panel member noted that she "didn't have problem" using uncertainty factor for background exposure. She remarked that background exposures were so rarely taken into account at risk management, it seemed appropriate for a chemical like TCE where background exposures were so high, that a default be included, if a particular population had no other exposure to TCE or metabolites or related compounds.

Another panelist commented that there was not a justification for choosing the 99th percentile as a point of departure. He expressed the view that the Agency's uncertainty factor for human variation for central nervous system effects for healthy workers was not sufficient for "kids'" risk. He wondered whether there were pharmacokinetic and pharmacodynamic data on the difference between adults and children.

A fellow panelist responded that children show greater toxic effects from TCE at all stages of absorption, metabolism, pharmacokinetics and pharmacodynamics, and that all evidence points to increased toxicity in

developing animals, compared to adults, for TCE and its metabolites. He said that it was critical to use a child uncertainty factor.

Another panelist spoke for the need for modeling, endpoint to endpoint, of pharmacokinetics for TCE and its metabolites that would provide information about human-to-human variability.

Panelists then touched on several different issues. One panelist expressed the view that EPA did not adequately justify reducing the uncertainty factor from 5000 to 3000; the Agency didn't identify which safety factor would be reduced. She called for a consistent approach between the RfD and RfC or explanation for the inconsistency. Another panelist mentioned that the document did describe the kidney toxicity endpoint well.

The panel Chair noted the paradox of TCE touched on by many panelists, that it is a chemical with much research very sophisticated modeling. One would think that such a situation would reduce uncertainty, but instead the draft assessment has an uncertainty factor of 3000. He stated that it was "incumbent on the Agency to show that having more data does not reduce uncertainty." The Agency needs to show, each step of the way, why research and analysis may not have reduced risk. The uncertainties need to be very carefully documented and described, so they can be explained to the public.

The Lead Discussant then commented that the Agency was proposing to do "something out of the ordinary" and needs to be on a firm foundation. In general, where the draft assessment breaks with precedent, it needs more rigor, more measurement.

The panel then briefly discussed the issue of TCE in breast milk. One panelist noted that this issue was briefly referred to in the draft assessment, but not described. She asked whether those levels should be considered as an uncertainty factor. The Lead Discussant responded that such information should into an exposure assessment, not be expressed as an uncertainty factor in the dose-response. In her view, "as technical folks we need to be as clear as possible about what the consequences of alternative choices should be." She urged fellow panelists to focus on identifying data-derived safety factors to achieve the Agency's risk management goals.

The Lead Discussant then summarized the panel's discussion of Question 4. She noted panel members' agreement on the importance of looking at multiple endpoints. She noted agreement that the hazard identification section needed attention, especially in the discussion of critical studies. She heard panel members call for more discussion of the cardiac endpoint and of the Fisher study. She noted that the panel disagreed on whether the Agency should set uncertainty factors that were relevant to all endpoints, or to develop them for individual endpoints. There may be common ground in a recommendation that the Agency better justify how it came to its conclusions in the face of different views in the scientific community. In general, she saw the panel urging that the Agency provide more information about non-cancer effects, so in the long term, risk managers could use the different kinds of risk assessment information to implement different environmental statutes and programs (e.g., ones designed to address varying degrees of variability and susceptibility).

Discussion of Charge Question 5: Does the assessment adequately discuss the derivation of a range of estimates for the cancer risk? Are there any studies that should/should not have been included?

The Lead Discussant began by saying that EPA's approach is original and that he didn't see many alternative approaches. One major study to add would be the Hansen study. He thought it was appropriate to express the estimate of risk as a range, although the Agency should express the rationale for the range chosen more clearly. He suggested that EPA's own "response to comments" document contained language that should be incorporated in the assessment

In his opinion, use of a range was supported by diverse studies and should not be condensed to a central tendency value, which always has some weighting and judgment factors built in

The Lead Discussant said he "would like better description" for the range chosen; it is not an interval estimate and not a concept based on population, sampled statistically. The range is not derived from a large sample, only three independent studies. The Agency needs to strengthen its description of how the range was described (its use of the term "robust" estimates was not so well described. The Agency could benefit from describing how GST, age, gender and exposure played a role in the ranges set.

He noted that the option of non-linear extrapolation is qualitative, not quantitative; it could become quantitative only if combined with mechanistic modeling, which is very difficult. He concluded that it is not possible to do nonlinear mechanistic modeling for TCE. In Figure 4.2., EPA tried to explain both the linear and nonlinear approaches. He commented that the "Safe dose discussion goes nowhere"-- if you combine linear and non-linear – you’re stuck with problem of choosing uncertainty factors. He cautioned the Agency to use great care to explain how the modeling was done.

The Associate Discussants then expressed their views. The first stated that non-linear extrapolation is used only if the mode of action is well understood, and that it is not well enough understood, even for liver carcinogenesis. He agreed that derivation of cancer ranges from available studies was not well described. Clearer descriptions should be given of: extrapolation from chronic oral studies; interaction among metabolites; use of human studies, given the lack of exposure information; availability of dose metrics; mode of action; body-weight scaling, and use of pharmacokinetically based physiological models. The Agency needs to outline more clearly the sue of the complex information needed to make the case for the different species of cancer and different metabolites involved.

He urged the Agency to clarify its use of the term "human susceptibility" and "human variability." He stated that the several risk estimates derived from a variety of factors reflect variation within different determinations and should be called "variability," not susceptibility.

The Second Associate discussant agreed that it was appropriate to express the risk as a range, because "a single number is artificial." He gave a "qualified yes" to the charge question asking if the rationale was "adequately discussed" because he was not able to review the primary papers involved.

He asked the Agency to keep in mind that its audience is the public, and that the document needs to be very clear. He stated that the document should have footnotes and definitions throughout, as it did in Chapter 1. He noted

several items in Chapter 4 that were unclear (e.g., Table 4.1. discussion about confidence intervals; wide difference between the results of the two PBPK models are not discussed). He expressed concern over the use of the Clewall model in the draft assessment, given Dr. Clewell's reservations concern over public commenters' inability to secure and reevaluate the Antilla data. He encouraged the Agency to invest in and strengthen the use of PBPK models for this and other risk assessments.

The third Associate Discussant criticized the data used to create an assortment of slope functions. Decisions to include or exclude a study have a big effect on the values chosen. He stated that using the German cohort values quantitatively for extrapolation "makes him uncomfortable." He recommended that the Agency use the Hansen study in a meta-analysis and "trade in for existing data." He said that he would "resist doing anything with kidney' because of the lack of strong data.

Another panel member then emphasized that "some presentation of range of evidence is step forward for EPA" and pointed it that the draft assessment's semi-quantitative acknowledgement of uncertainty is a "giant step forward." He stated that it was "really important" to have the derivation of each of the numbers presented more clearly. Section 4 is too terse. People should be able to reproduce the Agency's numbers; it would be helpful to have EXCEL spreadsheets available to facilitate the calculation.

He then noted a troubling aspect of the current presentation, which seems to calculate Finnish urinary cancers only on the basis of cancer cases, not population at risk, not just folks who got the cancers. He also asked if the Agency, in examining the occupational epidemiological basis of cancer corrected for the healthy worker survivor effect. This adjustment can change the baseline; it needs to be done in a way that meets the standards of epidemiological analysis, otherwise a bias is introduced. He also noted that it was unclear whether the Agency was presenting best estimates or upper bounds in its analysis of the Antilla.

Another Panelist asked how should the Agency incorporate the strength of evidence into the assessment. A fellow Panelist responded that an integrated assessment required an integrated subjective assessment of likelihood. The most comprehensive technique is expert elicitation, but "it has its problems." He had conducted such a process for chloroform, but it was "not easy to do in a highly charged and politicized atmosphere. What is needed is a way experts can fairly communicate what their "state of the world" is likely to be, in a disciplined, finely calibrated way.

The discussion then turned on how to conduct integrated assessments without this expert elicitation -- without them, in one panelist's view, the Agency doesn't use information available. Another panelist responded that it is helpful, when developing risk ranges, to give users confidence intervals, along with risk management guidance, that might indicate when it is most appropriate to use mean values, or when to high end values with confidence intervals.

A question from the public then raised the issue of past Agency practice using epidemiological data for risk assessments and emphasized the weakness of epidemiological information, given the lack of exposure data. An panelist responded that the strengths and weaknesses of epidemiological data needed to

be compared with the strengths and weaknesses of toxicity data, which often had a 15-to-20-fold adjustment from animals to humans.

The discussion concluded as the Lead Discussant summarized the panel's views. He heard no objections to the draft assessment's use of a range, but a need to better describe the rationale for the range chosen. This rationale would be detailed for different cancer sites; explain each study; and give reproducible numbers, and full documentation. He heard consensus that the use of PBPK modeling and analysis of modes of action involved a new paradigm that called for additional research. There was also a call for a reanalysis of the Finnish study. There was agreement that the Agency provide readers with a way to reproduce its analysis, perhaps by giving them access to a supplementary EXCEL spreadsheet with the data used.

The Panel Adjourned at 5:15 pm

Wednesday June 19, 2002

The Chair began the discussion on Day 2 at 9:00 am

Discussion of Charge Question 9: Do the data support the possibility that TCE can affect children and adults differently? How can this be reflected in the quantitative assessment?

The Lead Discussant began by stating that although key studies were not completed yet, it was appropriate to add an uncertainty factor for differential risks for children, given suggestive studies completed. His most serious concerns were for neurotoxicity effects, birth defects in the eye, and hepatotoxicity. He saw some susceptibility to cancer. The Lead Discussant thought it was appropriate to factor in the issue of cumulative effects, since TCE exposures might be exacerbated by alcohol exposure during pregnancy and by some drug interactivities. He saw it as appropriate to draw links in the document between the pregnant female mouse and human female.

He suggested that the document systematically discuss chloral hydrate, methanol, and all major metabolites of TCE systematically. He called for each section of the document to examine risk implications for children. He called for a full treatment of the toxicity data and the many studies of the human newborn, as well as an examination of what is not known (e.g., "nobody's looked at the exposure of developing mammalian reproductive function in long term). He noted that EPA documents often mention that children metabolize drugs faster than adults; he said that such generalizations should be examined in the light of data and that this statement was not generally true.

The Associate Discussant then contributed her views. She stated that, in general, age-related toxicities could vary. Infants and children generally receive greater exposure through respiration and absorption through the skin and that impacts are greater in perinatal exposure. She concurred that that the document should examine children's issues throughout, and also suggested that the Agency's exposition of the differential hazard for children would be better presented if material was also integrated into 1 section devoted to a discussion of risks to children. She said that the 50 fold safety factor

includes protection for children and that the issue of risks to children was an extremely important area for research.

Other Panelists then entered the discussion. One Panelist suggested that the draft assessment could benefit from data on vinyl chloride regarding differential risks. He added that it would be helpful, wherever possible, to quantify information about differences between adults and children. One difference that could be quantified is information about metabolism patterns. Another Panelist stated that the mix of metabolites can make a big difference and that a child's metabolism can differ quite dramatically, depending on compound involved.

Another Panelist raised a question about the Wilson study that involved cardiac malformation. She had a concern about the body of evidence mounting about cardiac malformations. The Wilson study, for example, asked questions about solvents and degreasing compounds, not TCE. She thinks the elevated results shown in this study may be related to solvents and mixtures; "we don't know it's TCE." She stated that the draft assessment should clarify where there are multiple exposures, and where there is a definite link to TCE. The Panel Chair then asked whether this uncertainty is one of the differences between the RfC and RfD. Another Panelist added that, even when you consider TCE by itself, it is a "one-chemical mixture."

Yet another Panelist asked how EPA's draft assessment dealt with differences between children's and adult's exposures -- when those are factored into susceptibility and when those are factored into the exposure assessment. Dr. Cogliano said that children's special dermal, inhalation, and ingestion exposures are factored into the Agency's exposure assessment and not factored in the RfD and RfC. He said susceptibility has 2 different components: higher exposures and higher biological susceptibility. The latter is incorporated in RfD and RfCs.

The Panelist responded that she heard the Panel saying "kids could have increased exposure" but that really isn't part of the hazard assessment. Susceptibility really should be focused on pharacokinetics and pharmacodynamics. She asked whether the risk assessment itself is conservative enough, and whether the 10-fold uncertainty factor is sufficient to cover variability in children. She did not think she has the best information to decide that an additional factor was necessary. She stated that she thought there was sufficient information on metabolism to figure out "how things come together" (e.g., the amount of TCOH formed, how it is metabolized) but such information is not presented in the draft assessment. She expanded this thought by stepping the group through the following reasoning: that if the Agency based the cancer slope on the kidney effect, (an item under debate), then added an uncertainty factor of 50, she had the sense that such an assessment was over—protective to begin with, and there was then less concern with adding another factor to protect children. For her, in evaluating the draft assessment, the question was not children's exposure; instead, it was "for a given dose are there pharmacodynamic or pharmokinetic data available to show a meaningful scientific response" indicated children's increased susceptibility.

The Lead Discussant responded that children showed lower clearance levels for TCE and its metabolites, and a higher body burden. They also showed intrinsic organ sensitivity. He pointed out that the central nervous system of the developing fetus was more sensitive generally. The Panelist responded that toxicology studies do not always show a higher susceptibility to neurotoxins for developing fetuses. Another Panelist commented that this situation might be a very appropriate one for use of an uncertainty factor because the purpose of an uncertainty factor is "to protect when we don't know."

The Chair then stated that the document should present more clearly quantitative data about differences. If the quantitative are not there, the Agency needs to explain why qualitative data drive uncertainty and why uncertainty factors are justified.

Another Panelist followed up to say that there is quantitative information on clearance differences and differences on body fat content. He also identified a need for developing a systematized database focused on the effects of neurotoxicants that would focus on the differential pharmacokinetics and pharmacodynamics of adults and children.

A different Panelist raised the issue that EPA has been inconsistent in its implementation of exposure scaling to account for children's increased exposures. The pesticide program is accounting for children's increased exposure, but rest of the Agency does not so much. She suggested that the draft assessment itself highlight more often where children's exposures are greater than adults are, as it does in the footnote on page 1-15. In regard to susceptibility, she said she understands that "people are not interested in adding another uncertainty factor," and that Panelists wanted to add language to 50-fold uncertainty factor to include children. She viewed that approach as reasonable based on the spectrum of variability for adults plus children, infants, and fetuses. On the other hand, she said that the Food Quality Protection Act often imposes a 10-fold uncertainty factor for kids. In the case of TCE, she saw affirmative indicators that infants and fetus are more susceptible. In addition, cardiac and opthamalogical teratology, plus observations of childhood leukemias "notch up the level of concern" for what may be going on and makes her nervous that overall assessment may not be adequately protecting kids.

Yet another Panelist linked the issue of protecting children to the cumulative risk issue. He saw the 3000-fold uncertainty factor as more than adequate. He suggested that EPA factor out the component devoted to protecting children and discuss that as a separate factor.

Another panelist focused on the difference in how the Agency treated the RfC and the RfD. He pointed out how they were derived using two different approaches that were inadequately explained. For the RfC, there is a 10-fold factor to accommodate adult variation alone; there is a 50-fold factor for the RfD. He posited that the Agency had done an inadequate job in discussing human variation in setting the RfC. The next speaker called the 10-fold uncertainty factor one of the "persistent mysteries" and wondered "what exact population is the 10-fold factor supposed to represent?" He would prefer that the uncertainty factor be expressed as something like 3 standard deviations.

The Lead Discussant captured the Panel discussion in his summary. He described the central issue as the uncertainty factor. He heard two approaches. One view suggested that there is sufficient PBPK and other evidence of children's increased to say there should be additional uncertainty

factor. Another view suggested that the uncertainty factors already in place are wide enough to protect children. The issue becomes further complicated because the uncertainty factors for the RfC and RfD are different.

One Panelist then interjected that the issue of uncertainty factors was linked to how the general risk assessment was constructed. If the Barton and Clewall endpoint-by-endpoint approach were taken, then she would be more open to use of an uncertainty factor for children.

The Lead Discussant then continued his summary. He saw agreement that there needed to be more discussion of risks to children and an integrated summary of children's issues. The Agency needs to discuss the evidence for susceptibility to developing organs, and then show how the assessment deals with this issue. He saw a need for attention to issues of children's risks in each section of the document and also an integrated summary in a children's chapter. The Panel agreed that this risk assessment, the first major document to be generated after Executive Order 13045, has a unique role in showcasing the Agency's approach to protecting children's health through risk assessment.

Discussion of Charge Question 6: Please comment on the use of calibrated models and uncertainty analysis to address the question of pharmacokinetic model uncertainty.

The Lead Discussant began by noting the significance of the Agency's use of calibrated models and uncertainty analysis. They represented a novel application by the Agency, even though there has been a long-standing call for uncertainty analysis. He identified a need for the Agency to explain modeling uncertainty very carefully, to explain the assumptions underlying parameter values, the data sets used, and how and why results from different models vary. It was important to convey the state of the art of the science of modeling clearly. He suggested that the Agency model as Bois did, then it needs to explain the basic features of the model in detail, preferably in an appendix. He suggested the Agency describe the biological information underlying the model, including male-female differences, the new data used for calibration, and the main references there, not just the State of the Science papers.

One additional issue involved "cleanness of data" and reproducibility. The Lead Discussant noted the concern over the reproducibility of results from the Agency's Bois calculation. He suggested that the Agency should make the data used available for analysis by others. Dr. Cogliano then clarified the Agency's long-term plan to develop a publicly available pharmacokinetic model framework that could be tailored to different chemicals. It would be available on the EPA website available and could be run in parallel with other models.

The Associate Discussant then provided her comments. She noted that the Agency used both the Clewell and Fisher models. She saw a need for the Agency to discuss how the differences in their structure, the different parameter estimations used, especially key sensitive parameters, and the differences in data sets used. She expressed concern over the data sets that could justify changing model structure in the Bois analysis. She suggested that the Agency conduct a basic test of the different models using similar data sets to evaluate goodness of fit and calibration; she didn't think that had been done.

She suggested that the Agency, within the assessment itself, identify the criteria for selection of the model used and say "up front" what model will

give the best estimate. She called for a table showing dose metrics for all endpoints considered and what datasets they were to be developed from.

She suggested that it be a good time for EPA to evaluate predictions between the Bois model and other calculations of risks.

Another Panelist suggested that the Agency's reliance on the "state of the science papers" might have posed a problem because of the limited length of those articles. The articles were not sufficiently detailed to make explicit the many details of the models discussed.

A second Panelist stated that if the Agency was going to base a risk assessment on a model, the model has to be available so experts can use them and check them.

A third Panelist stated that the Agency should be commended for including a discussion of PBPK modeling discussion in the draft assessment. He noted a large difference in results between the two models discussed. He noted how Bois had enhanced model use with the Markov chain methodology. He suggested that the Panel definitely encourage application of such techniques. He supported the view that reproducibility was critical and that the Agency should provide the information and data sets so that other people can peer review and critique the analysis.

Another Panelist called for a clearer "tracing" of results of different models that would clarify the different results. He called percentiles for dose metrics, means and not just medians. He underlined the concern of Dr. Clewell about the use of the model by Dr. Bois and asked whether "posterior distribution have wandered from prior distribution that original authors had put in." He stated that he needed to better persuaded by a more extensive discussion of how new experimental data, added to the model, might be changing the outcome. "Clewall's comments deserve a hearing and maybe recalculation; Bois is the most sophisticated person in field, but he can be wrong." He also called for a systematic approach diagnosing the problem. He was not happy with using the wide uncertainty associated with the draft assessment as a justification for throwing out the modeling results for kidney cancer. He called for the Agency to use a systematic approach for weighing the animal results vs. epidemiology findings.

Then a Panelist asked whether Section 4.5.7., which focused on model and parameter uncertainty and uncertainties associated with epidemiology data and how those were used, should also deal with uncertainties associated with exposure modeling. Another Panelist agreed and said that the Henschler study might have average exposures 2-to-3-fold higher than the 50 ppm generally assumed as average exposure, or 2-to-3 fold lower. He stated that those differences might explain some of the differences in modeling results.

The Lead Discussant then summarized the Panel Discussion of Charge Question 8. He stated that the Agency needed to clarify the differences between its application of the Clewall and Fisher models. There is a need to describe the models used, what each involves, and what it can and cannot do. There is a need to explain the 15-fold difference in results, and the impact of dose metrics on modeling results. He heard a call to encourage EPA to proceed in the use of PBPK modeling, and to take the serious effort and time necessary to develop this approach. The Agency will need to provide specifications and assumptions for the model structure and provide access to the data used.

Discussion of Charge Question 7: Is it appropriate to consider background exposures and other characteristics of an exposed population as modulating the risk of TCE exposure in that population?

The Lead Discussant identified the broad range of exposures that could be included in this charge question, e.g., exposure to TCE metabolites, to TCE-like chemicals, such as other solvents, to ethanol, or to incense. There is also the issue of genetic variability, including GST variability and AT heterozygotes. And there is also the issue of the medical condition of an exposed population's medical conditions (e.g., diabetes, AIDS, Non-Hodgkins lymphoma). He suggested that experience with radiation offered a precedent to draw from; factors most useful to consider are those that are constant and clearly show a relative risk.

He suggested that it meant sense to consider exposures for similar metabolites, but not for medical conditions.

The Associate Discussant began her discussion by acknowledging that humans are not exposed to TCE in isolation. She thought it was appropriate to consider background exposures to TCA and DCA and other compounds that have similar metabolites and to consider other exposures that could modulate reaction to TCE. She focused on the question of how one would adjust for these co-exposures. She noted that EPA chose apply a modifying factor of 3 to the RfD for co-exposures to common metabolites. She asked whether the uncertainty factor for human variability account for age, lifestyle factors, drugs or whether there needs to be an additional factor. She believed it is probably included for the RfD, but the RfC does not include a modifying factor, probably because the RfC was developed from human data where other exposures were built in.

Another Panelist identified herself as essentially in agreement. She broke down the different factors under this question into categories: (1) exposure to the presence of TCE from other sources than one at issue; (2) chemicals other than TCE that are haloacetic acids or metabolized like perclorethylene; (3) external factors like medications or ethanol; and (4) disease factors or other host factors (e.g., CYP2E1) in the adult population. She viewed some of these factors as falling under questions of exposure and others falling under the category of human variability.

She saw merit in building in an uncertainty factor in the risk assessment for these factors rather than leaving them to risk managers. She expressed the view that including a "background uncertainty factor" in the RfD was responsive to public health and community groups. She saw why 3-fold background factor would be added for RfD, and omitted from the RfC, derived from epidemiological data, but was concerned about the RfC, because intrinsic was not factored in. She encouraged the Agency to "beef that up"

Another Panelist expressed the view that the suggestions of the last two panelists, in general, were sensible. It was appropriate to develop some uncertainty factors for background exposures, but the task would be overwhelming without classification of categories. He stated that he thought there wasn't on exposures, but the typology advanced by the last discussant offered a way to break down different categories and offer considerations

Another Panelist agreed that the Agency must consider "more typical exposures" and that "reality is mixtures...multiple exposures." He suggested

that the Agency begin such analysis with a finite system, biological and look at factors perturbing the system. His laboratory used a reaction network modeling approach, drawing on experience of petroleum engineering, to range from the physiologically level, to the pharmacokinetic and molecular levels.

Yet another panelist asked whether such factors for background exposures should be done as part of the RfD. She rejected the rationale she had heard expressed that it was desirable because risk managers do a poor job of considering background exposures. She called on fellow panelists to develop a scientific, not a policy-based response to the question. She called for an expanded version of Table 2.1., which drew more fully on knowledge of genetic and metabolism to provide a good discussion of how background impact the risk of exposure levels. She stated that science is further along than the language in the draft analysis suggestions.

She also suggested that the issue of background exposure needs to be addressed carefully, along the lines of the guidance being developed on cumulative risk. She stated that it was "too important to do on the fly on this." She also reminded the group that RfDs were used to compare across chemicals; in her view, to develop RfDs inconsistently was probably more damaging than to wait to develop a consistent approach. In any case, she stated that the Agency needed to improve the discussion of how uncertainty factors for background exposures were developed.

The Panel Chair then stated that the section on background exposures was important and needed to be strengthened. The generic issue was that there were "lots of chemicals out there interacting." He asked the Panel to focus on contributors to TCE risk and set aside the broader issues. He suggested that where exposures were ubiquitous, and non-voluntary, there was a need to consider what part of this background exposure can be accounted for. And if smoking is prevalent and relevant, then it needed to be addressed.

A Panelist reflected that she heard the panel agreeing that greater attention should be paid to relevant background exposures affecting TCE toxicity and that an additional uncertainty factor of 3 was appropriate. Panel members have varying opinions about the appropriate science-based response. She called for the panel response to this question to separate issues.

The Lead Discussant then summarized the Panel's conversation. He heard agreement that the Agency should discuss and account for background TCE, DCA, other metabolites, and other chemicals that metabolize to those metabolites. He heard agreement that the Agency should list those chemicals and provide more detail about what they metabolize to and to what levels, and whether and how there is measurable impact on TCE risk.

He heard that the 3-fold safety factor for RfD needs some justification. There is much data on TCE, and the Panel is asking the Agency to discuss what can be done using these data to assess whether 3-fold factor is appropriate.

For other exposures, such as medication, and listing of SIP 2e1, there is a need for discussion of the impacts of these exposures.

If there is a central safety factor accounting for ubiquitous exposure, The Panel would trust risk managers to make appropriate adjustments for additional risks. The group also agreed on the importance of quantitative research in this area

Discussion of Charge Question 8: Do the data support identifying risk factors that may be associated with increased risks from TCE exposure? Are there any risk factors that should/should not have been included?

The Lead Discussant acknowledged that many relevant issues had been discussed in the context of Charge Question 7. She emphasized the importance of precise, quantitative information to shed light on this question. For example, she discussed the issue of timing of exposures, so as to measure more precisely fetal exposures, since the fetus is capable of metabolizing compounds earlier than mice and rats and was probably acting as sink absorbing TCE. She called for measurements of exposures through breast milk to estimate the total body burden in a baby's first year, and also called for exposure to infants through tap water used in mixing formula. She called for thorough attention to risks to children throughout the document.

Other areas that needed attention included male reproductive effects.

Fellow panelists identified other areas for attention in the document including variability and susceptibility by ethic group and genetic area polymorphisms.

(The Panel then had a working lunch, where Dr. Yang, a panelist, by request, provided a discussion of mixtures and risk assessment. He discussed work conducted at Center for Environmental Toxicology and Technology at Colorado State University. He reported results of toxicity studies on a mixture of several compounds, including 111-trichloro ethane, perclorethylene, and TCE, conducted with a PBPK model. He advocated for research on mixtures, including mixtures at low doses.)

Panel Discussion of Consensus Findings

The Panel Chair opened the discussion by asking panel members for pressing issues to discuss before the group identified next steps and key points for its cover letter to the Administrator.

Several panel members asked for clarifications. One panelist asked whether an LED 10 was a no-effect level or low-effect level. Dr. Vanessa Vu answered that it was an apparent, not true NOEL. Another panelist asked that if one calculated an LED 10 from the developmental literature, the number closest to what they think is equivalent to NOEL, it would be 3-fold lower than the NOEL. The Agency, however, is choosing a benchmark dose and "somewhat penalizing" a better approach.

The Panel Chair said the definitions used in the Agency's non-cancer approach were confusing within the draft assessment and across Agency documents. Dr. Vu seconded that view and said it was confusing to use an old paradigm with the benchmark dose. Dr. Cogliano said that the approach to use would be determined by the "what underlying data you have." A Panelist responded that she would address the issue of inconsistencies in her write-up.

The Panel Chair pointed out that this issue is another case of how the draft assessment "goes beyond where the Agency is" on multiple fronts. He has heard the Panel ask for more consistent guidance to support such bold assessments as this draft TCE assessment.

Panel Discussion Of Next Steps

The Panel Chair outlined a proposed schedule for development of the panel report:

1. Lead discussant composite write-ups to the DFO by Friday June 21
2. DFO to send draft minutes to chair by June 24
3. DFO to send integrated set of write-ups (first draft of panel report) to panelists BY June 28 (if possible to Drs. LeMasters, Blair, and Solomon by June 27th). Chair to have reviewed document beforehand.
4. Panelists to send comments to DFO by July 8 and to include specific language for recommended changes
5. SAB Staff to post revised draft on SAB website on July 12 and send to panelists
6. DFO to send Agenda for Public Teleconference and identify process for submitting written comments before July 18 Teleconference
7. Public Teleconference on July 18
8. Revised document to Panelists for review
9. Revised Panel report to SAB Executive Committee.

The Panel agreed to this schedule. The Chair emphasized that Lead Discussants should reflect the multiple perspectives heard at the meeting in their write-ups. It would be appropriate to indicate disagreement in the following ways: "one member disagreed, one member stated a (different) view; several members..., a consensus of the panel." The Chair also asked Lead Discussants to identify research recommendation within their write-ups and to identify, short term v. long term research.

Panel Discussion of Key Points for Cover Letter

The panel agreed on the following key points:

1. The Agency should move ahead with the document. The Document is a good starting point. The Panel commends the Agency for its effort and advises it to proceed.
2. The Agency should be commended for its groundbreaking work in the following areas: children’s issues; susceptibility cumulative risk; use of modeling; explicitly recognizing/acknowledging uncertainties; use of multiple endpoints for derivation of RfD; examination of multiple modes of action; multiple metabolites.
3. Acknowledge these new areas are major new areas of work and progress in them will involve an evolutionary process. More thorough exploration may change some of the values that appear in the draft document. There is a need for guidance in many of these areas.
4. Because the document breaks ground in many areas, there is a need to strengthen the scientific basis for the document, a need to improve the rigor of the discussion improved
5. Controversy has come with progress in these new areas; public comments have raised many valid concerns that the Agency has to carefully

address. Panel urges the Agency to review and address public comment, especially those from the "state of the science" authors

6. key areas of controversy include:
   a. use of epidemiology data (its use for the slope factor; the need to update the related uncertainty analysis; the need to incorporate new studies; the need to focus on first tier studies)
   b. the need to develop a more formal way of selecting and weighing evidence and communicating those decisions, when evidence comes from multiple lines of evidence
   c. Agency's treating cancer mode of action in a linear way
   d. the need to explain derivation of the RfD and RfC study by study, endpoint by endpoint
   e. The need to quantify and provide more explicit justification for factors relevant as background exposures that should be included as safety factors incorporated in the TCE assessment

7. There is a need for a summary paragraph in each section describing the Agency position and clear description in each section of scientific basis for those choices and other alternatives considered.

8. There is a need for a new section to consolidate the assessment's conclusions regarding children's health. The new section should offer a model for other documents to follow. It would integrate information about specific aspects of risks to children's health as discussed in separate chapters

9. There is a need to improve reproducibility of the findings in the draft assessment; a need for the assessment to reference original papers on key issues, not review articles; and a need to provide access to data from which the Agency's modeling results can be recreated.

At 2:30 p.m., Dr. Anderson adjourned the meeting.
Respectfully Submitted:

Designated Federal Official
Certified as True:
Chair

NOTE AND DISCLAIMER: The minutes of this public meeting reflect diverse ideas and suggestions offered by the Panel members during the course of deliberations within the meeting. Such ideas, suggestions and deliberations do not necessarily reflect definitive consensus advice from the Panel Members. The reader is cautioned to not rely on the minutes to represent final, approved, consensus advice and recommendations offered to the Agency. Such advice and recommendations may be found in the final advisories, commentaries, letters, or reports prepared and transmitted to the EPA Administrator following the public meetings.

Attachments:

Attachment A: Panel Roster
Attachment B: Federal Register Notice
Attachment C: Sign-in Sheet
Attachment D: Meeting Agenda
Attachment E: Draft Document, "Overview of Panel Formation at the EPA Science Advisory Board"
Attachment F: Biosketches of Panelists
Attachment G: Slides and Materials Presented by Public Commenters